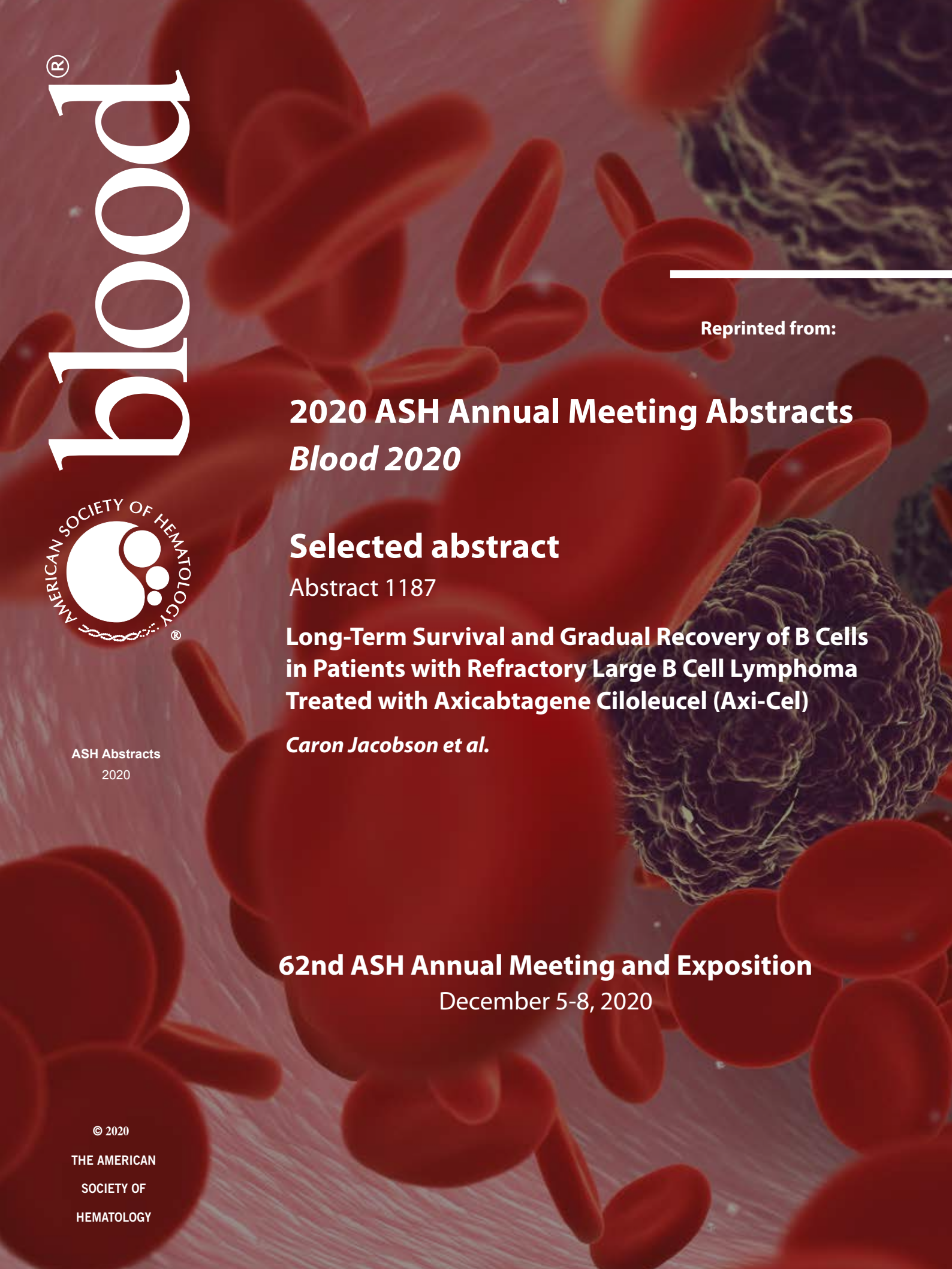

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Caron Jacobson et al.

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Abstract 1187

Long-Term Survival and Gradual Recovery of B Cells in Patients with Refractory Large B Cell Lymphoma Treated with Axicabtagene Ciloleucel (Axi-Cel)

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Background: Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy approved for the treatment of patients (pts) with relapsed/refractory large B cell lymphoma (LBCL) with ≥ 2 prior systemic therapies. ZUMA-1 is the multicenter, single-arm, registrational Phase 1/2 study of axi-cel in pts with refractory LBCL. In a 2-year analysis of ZUMA-1 (median follow-up, 27.1 months; N=101), axi-cel demonstrated objective response, complete response (CR), and ongoing response rates of 83%, 58%, and 39%, respectively (Locke et al. *Lancet Oncol.* 2019). Here, we present additional survival follow up and recovery of normal, polyclonal B cells from ongoing responders in ZUMA-1.

Methods: Eligible pts with refractory large B cell lymphoma (diffuse large B cell lymphoma, primary mediastinal B cell lymphoma, transformed follicular lymphoma) underwent leukapheresis at enrollment and subsequently received low-dose conditioning chemotherapy (fludarabine and cyclophosphamide) followed by a target dose of 2×10^6 anti-CD19 CAR T cells/kg (Neelapu et al. *NEJM*. 2017; NCT02348216). The primary endpoint was objective response rate (ORR), and the first response assessment was 4 weeks post infusion. Response assessments were performed per protocol up to 24 months or disease progression, whichever occurred first. For pts in ongoing response beyond Month 24, response assessments continued per institutional standard-of-care (SOC). Blood levels of CAR T cells were quantified using polymerase chain reaction and B cells were characterized using flow cytometry in pts with ongoing responses and evaluable samples.

Results: A total of 111 pts were enrolled, and axi-cel was administered to 101 pts. As previously reported in the ZUMA-1 2-year analysis, among pts who received axi-cel, the median time from axi-cel infusion to both objective response and CR was 1.0 month (range, 1 – 12 months; Locke et al. *Lancet Oncol* 2019). When the entire enrolled population (N = 111) was included on an intent-to-treat basis, the median manufacturing time was 17 days (range, 14 – 51; n = 110 as manufacturing was not feasible for 1 pt). Additionally, among the 111 pts, the median time from enrollment/leukapheresis to objective response and CR was 1.7 months (range, 0.7 – 12.9) and 1.9 months (range, 0.7 – 13.3), respectively. Responses have been durable, and with a minimum of 3 years of follow-up (median, 39.1 months), the median overall survival (OS) was 25.8 months, and the 3-year OS rate was 47%. Importantly, no axi-cel–related secondary malignancies have been reported.

As previously reported, pts in ongoing response after 2 years had significantly greater peak CAR T cell expansion in blood 7 – 14 days after axi-cel infusion than did those with relapse ($P = 0.014$) or no response ($P = 0.0003$; Locke et al. *Lancet Oncol* 2019). Blood samples from 22 pts in ongoing response (per institutional SOC) at ≥ 3 years were available for analysis of CAR T cells and evaluation of B cell recovery. All evaluable pts had detectable B cells in blood at 3 years post axi-cel. Notably, 91% of pts in ongoing response at 3-year follow-up demonstrated recovery of polyclonal B cells measured by presence of both kappa and lambda light chains on non-malignant CD19+CD20+ B cells. The median kappa-lambda ratio of 1.6 and relative levels of key B cell subsets, including memory and naive B cell immunophenotypes, suggested reconstitution of B cell repertoire, consistent with published data from healthy individuals (Deneys et al. *J Immunol Methods* 2001; Scott et al. *J Clin Pathol* 2018). Additionally, 15/22 (68%) had both minimal levels of detectable CAR gene-marked cells and detectable polyclonal B cells in blood. Altogether, these findings support the hypothesis that persistence of functional CAR T cells is not necessary for durable remissions of LBCL. Overall survival and translational findings with ≥ 4 years of follow-up will be presented.

Conclusions: Axi-cel produced rapid responses and longterm disease control in pts with refractory LBCL. Most responses occurred by the first assessment, and the brief time elapsed between enrollment and response supports both the speed and success of manufacturing. Furthermore, axi-cel–treated pts with ongoing responses at ≥ 3 years showed evidence of restoration of a normal B cell compartment and clearance of functional CAR T cells, a critical component of the long-term safety of CD19-directed CAR T cell therapies.

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